

# BioXyce: An Engineering Platform for the Study of Cellular Systems

Elebeoba E. May<sup>1</sup> and Richard L. Schiek<sup>2</sup>

**Short Abstract** — Many researchers use constructs from the field of electrical engineering for the modeling and analysis of biological systems [1,2], but few draw on and exploit parallels between electrical and biological circuits for simulation purposes. We develop a biological simulation system using Xyce<sup>TM</sup>, a large-scale electrical circuit simulator. BioXyce is capable of simulating whole-cell and multi-cellular systems. We present simulation results for *Escherichia coli* K12 central metabolism and cellular differentiation in *Drosophila melanogaster*.

**Keywords** — Large-scale biological circuit simulation, Xyce

## I. INTRODUCTION

ELECTRICAL systems, like biological systems, are composed of large numbers of components and interacting subcircuits. Simulation of these systems must produce accurate results in an efficient manner. Parallel circuit simulation tools, such as Xyce (<http://www.cs.sandia.gov/xyce/>) allow engineers to model and test very large-scale systems. The theoretical framework used in developing Xyce also provides the necessary tools for constructing a biological circuit simulator that can model multivariate, multiscale, hybrid biological networks.

In order to take advantage of the Xyce simulation framework, we create circuit abstractions of biological elements and construct netlist files that are executed using Xyce. Similar to the abstractions used in flux balance analysis (FBA), the flow of metabolic and genetic substrates is synonymous to the flow of current through an electrical circuit [2,3]. Metabolic reactions are simulated using analog subcircuits, where metabolite accumulation and degradation are modeled using capacitors and resistors, respectively. Genetic regulatory networks are modeled using Boolean kinetics and the enzymatic products of genetic pathways function as “metabolic clocks” by controlling when metabolic reactions occur; when the enzyme level reaches a pre-defined threshold, the associated reaction occurs. Boolean simulation of gene networks is consistent with the Boolean network models for genetic regulation used by other researchers [3,4].

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<sup>1</sup> Computational Biology Department, Sandia National Laboratories, Albuquerque, NM 87185 USA. E-mail: [emay@sandia.gov](mailto:emay@sandia.gov)

<sup>2</sup> Electrical and Microsystems Modeling Department, Sandia National Laboratories, Albuquerque, NM 87185 USA. E-mail: [rlschie@sandia.gov](mailto:rlschie@sandia.gov)

## II. WHOLE-CELL, MULTI-CELL, AND HOST-PATHOGEN SYSTEMS

Using these primitives, we perform whole cell simulation of metabolism in *E.coli* K12 and demonstrate the ability of our tool to simulate hybrid systems, such as the genetic regulation of central metabolism [3]. Large-scale simulations, which we demonstrate in a multicellular simulation of *Drosophila* development, allow *in silico* analysis of multicellular systems and provide a computationally tractable approach for analyzing the macro-scale impact of microscale events for systems biology applications. Leveraging BioXyce's ability to simulate whole-cell and multi-cellular systems we are using the circuit-based framework coupled with experimentation to investigate the impact of pathogenetic genes on the latency/reactivation phase of tuberculosis infection.

### A. Overcoming the Data Challenge

Constructing circuit netlists for large-scale system biology models can be tedious and time consuming. We have developed software tools that automate this process for metabolic and gene networks in a flat format. We are expanding these tools to enable BioXyce to construct organism-specific netlists using public databases such as KEGG, MetaCyc, and BioCarta.

The incorporation of empirically derived kinetic rates is an important challenge in constructing useable biological models. For metabolic networks with known rates, kinetic parameters for the metabolic models are imported from BRENDA and unresolved or conflicting rates are deduced using Dakota, a parallel optimization tool that is coupled to Xyce. The ability to execute Dakota and Xyce in parallel allows us to perform large-scale parameter studies using experimental data to formulate the objective function.

Successful development of an engineering framework for the study of biological systems can provide new insights on the regulation of complex cellular processes and elucidate information pathways relevant to host/pathogen interactions.

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